Brain Imaging and Psychiatry

PET imaging and cognition in schizophrenia

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C D Frith PhD **K J Friston** MRCPsych
P F Liddle MRCPsych **R S J Frackowiak** FRCP
MRC Cyclotron Unit, Hammersmith Hospital, London W12

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Introduction

The principal challenge for our understanding of schizophrenia is to trace the paths that lead from brain abnormalities to bizarre disorders of behaviour and experience. To take the first step on this journey we must devise experimental techniques which provide objective markers of abnormal behaviour and experience. This, in turn, requires that we construct models of the deviant cognitive processes that underlie abnormal behaviour and experience in schizophrenia. We have proposed such a model for two types of schizophrenic feature[1].

Defects of willed action

We suggested that certain negative features of schizophrenia (such as poverty of speech, flattening of affect and social withdrawal) reflect a defect in the initiation of willed acts. Patients with negative features can act when the appropriate response is triggered by an environmental stimulus (eg replying to a question), but cannot act spontaneously (eg do not elaborate their answers or speak spontaneously). Thus one of two possible routes to action is impaired in these patients (see Figure 1). This problem can be studied experimentally by requiring subjects to choose responses in the absence of any relevant stimuli. This is the case in the two-choice guessing task in which subjects have to guess whether a tossed coin will land on heads or tails. In this task normal volunteers produce a random sequence of guesses. In contrast, schizophrenic patients with negative features produced stereotyped sequences consisting of alternations or perseverations[2]. This result has been replicated by Lyons and her colleagues[3,4] who pointed out the similarity of this behaviour to that shown by rats treated with amphetamine. On the basis of a number of animal and human studies, Robbins[5] has proposed that willed action depends upon a fronto-striatal system in which dopamine plays a crucial role.

Defects of self-monitoring

We have suggested that certain positive features of schizophrenia (delusions of control, thought insertion, auditory hallucinations) also involve willed actions, but in this case the defect lies in failure to monitor

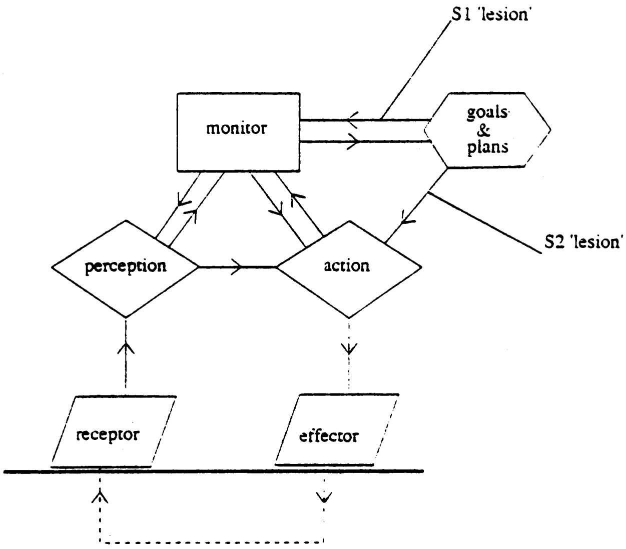

Figure 1. The initiation and monitoring of action. Schizophrenic patients with negative features (S2) have difficulty initiating actions from goals and plans. Schizophrenic patients with positive features (S1) initiate actions, but do not monitor these initiations

the intention to act, rather than in initiating such acts (see Figure 1). As a consequence of this defect, the patient finds himself carrying out acts without awareness of an associated intention. Such acts will clearly be perceived as alien.

Having awareness of our intentions as we carry them out enables us to make rapid error corrections. We can observe that we have initiated the wrong response and do not need to wait for peripheral feedback to provide this information. This ability can be studied in simple tasks in which subjects track a target on a VDU by moving a joystick. Many studies of this sort[6] have shown that people can correct errors in such tasks in the absence of visual feedback and at a speed that is too quick for the error correcting response to have depended on kinaesthetic feedback. Thus error correcting ability in these tasks provides an index of the subject's use of the central feedback loop and, hence, of his ability to monitor his own actions. Malenka and his colleagues[7] observed that schizophrenic patients made significantly fewer error corrections than controls when peripheral feedback was not available. Frith and Done[8] found that patients with passivity experiences (eg delusions of control, thought insertion) failed to make error corrections in the absence of visual feedback, while psychotic patients without these particular symptoms performed normally. These experiments provide some evidence that a defect of self-monitoring underlies certain of the positive symptoms of schizophrenia. An attempt to relate self-monitoring to a particular brain system must be extremely speculative. Frith and Done[8] suggested that the hippocampus might be involved, on the grounds, first that awareness of one's current intentions is part of 'working memory' for which an intact hippocampus is believed to be necessary[9] and, second, that the hippocampus has a role in a system

Correspondence to: Dr C D Frith, CRC Division of Psychiatry, Watford Road, Harrow HA1 3UJ

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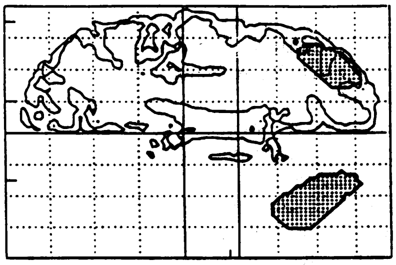

Figure 2 (a)

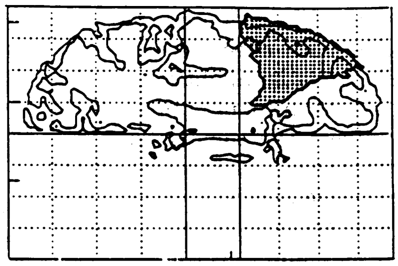

Figure 2 (b)

Figure 2. (a) Increased blood flow associated with self-generated finger movements is seen bilaterally in dorsolateral prefrontal cortex. Significant changes are shown superimposed on the corresponding horizontal slice from the stereotaxic atlas of Talairach and Tournoux[15] 20 mm above the AC-PC line. (b) Increased blood flow associated with self-generated words is seen in left dorsolateral prefrontal cortex. Significant changes are shown superimposed on the corresponding horizontal slice from the stereotaxic atlas of Talairach and Tournoux[15] 20 mm above the AC-PC line

which compares the intended and the actual state of the world[10].

Linking cognitive processes and brain systems

Having specified two cognitive processes that may be relevant to certain signs and symptoms of schizophrenia, we are able to take the next step on our journey towards the brain. Positron emission tomography provides a unique methodology for relating cognitive processes to brain systems. Posner and his colleagues[11] have shown how this technique can be used to relate brain systems to operations concerned with single word processing. We have recently begun a series of studies using PET in normal volunteers to investigate cognitive processes relevant to schizophrenia.

Brain systems and willed action

In order to highlight the brain system associated with willed action we contrasted a task based on the two-choice guessing task with one in which the subject did not have to choose which response to make. In the control task the subject felt a random sequence of touches to either the first or second finger of his right hand at a rate of 1 per 2 seconds. In the task requiring willed action, the subject felt the same series of random touches, but this time he had to lift a finger 'at random' and thus not necessarily the one that was touched. Thus his task was to generate a random sequence of finger movements, with touches to the fingers indicating when the movements were to be made. Thus in both tasks, the subject's fingers were touched in a random sequence and he moved his fingers in a random sequence. The difference between the tasks is that in one the response is determined by the stimulus while in the other it has to be self-generated by the subject. Differences in regional cerebral blood flow (rCBF) between the tasks will reveal brain regions associated with self-generated responses. In a study of six normal volunteers, we observed this activity to be in the dorsolateral prefrontal cortex (see Figure 2a) and anterior cingulate cortex. We have performed a parallel study on another six volunteers in which words were generated rather than finger movements. In this experiment also dorsolateral prefrontal cortex was activated, but this time on the left only (see Figure 2b). Both the experiments are described in detail elsewhere[12].

Brain systems and self-monitoring

We have now completed a pilot study in which we attempted to highlight brain areas associated with self-monitoring. We could not use the error-correcting task[8] for this purpose, since, in this task, self monitoring is only required when the subject makes errors. These occur infrequently. For a PET study we require that the self-monitoring process be engaged continuously as far as possible throughout the 2 min of the scan. Teuber[13] has suggested that central monitoring is required when subjects have to adapt to sensory distortions (eg while wearing prism spectacles). In order to adapt to the distortion the subject must compare the *intended* movements of his limb with where he *sees* the limb moving. We chose to study eye movements, because we have minimal awareness of eye movements except via what we see[14]. In order to distort the relationship between intended eye movements and sensation, we used EOG signals to drive a VDU. When the subject moved his eyes to the left of the VDU, this caused a target displayed on the VDU (a large diamond) to move to the right. The subject's task was to move the diamond from side to side of the VDU at the rate of 0.5 Hz. In this task the effect of eye movement on visual input was distorted and the subject had to monitor his intended eye movements in order to control the movement of the target. Two control tasks were also used. In the first control task, the target moved from side to side at the rate of 0.5 Hz while the subject kept his eyes still. In this task there is 'real' target movement, but no eye movement and no distortion. In the second control task, the subject moved his eyes from side to side at the rate of 0.5 Hz while the target remained stationary. In this task there is eye movement, but no 'real' target movement and no distortion. In the experimental task there was 'real' target movement, eye movement and distortion requiring the subject to monitor his intended eye movements.

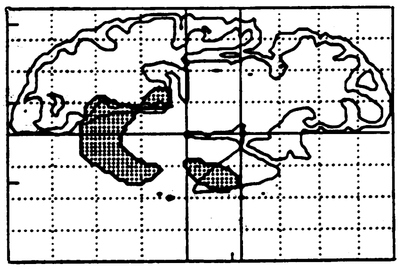

Figure 3. Increased blood flow associated with central monitoring of eye movements is seen in the left hippocampus and in parahippocampal cortex. Significant changes are shown superimposed on the corresponding horizontal slice from the stereotaxic atlas of Talairach and Tournoux[15] at the level of the AC-PC line

Thus, subtraction of the two control tasks from the experimental task would eliminate effects of eye movement and target movement, but highlight brain activity associated with the monitoring of intentions. In a study of six normal volunteers, this comparison highlighted extra-striate cortex, the parahippocampal gyrus and the left hippocampus (see Figure 3). When we examined changes over time, which should reflect adaptation to the distortion, we found that the left hippocampus was especially activated during the first experience of the visual distortion. We suggest that the activity in the extra-striate cortex reflect the specifically visual nature of the task, while the hippocampal activation is related to more general aspects of self-monitoring. If this account is correct, then a task in which auditory feedback is distorted should activate hippocampal areas and auditory cortex.

Conclusion

We have used PET to identify brain systems involved in some of the cognitive processes underlying signs and symptoms of schizophrenia. We would expect patients who persistently manifest particular signs and symptoms to show abnormalities in precisely these brain systems (see Liddle *et al.*, below). The tasks we have developed can now be used to elicit abnormal cognitive processing in schizophrenic patients while they are being scanned. Such studies will reveal the disturbed brain systems associated with these cognitive abnormalities.

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Cerebral blood flow and mental processes in schizophrenia

P F Liddle MRCPsych[1] **K J Friston** MRCPsych[1,2] **C D Frith** PhD[1] **R S J Frackowiak** FRCP[1]
[1]*MRC Cyclotron Unit, Hammersmith Hospital, London, and* [2]*Charing Cross and Westminster Medical School, London W6*

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Summary

The patterns of cerebral blood flow associated with three syndromes of schizophrenic symptoms are compared with the loci of cerebral activation in normal subjects during the performance of mental processes implicated in the three syndromes. The psychomotor poverty syndrome, which has been shown to involve a diminished ability to generate words, is associated with decreased perfusion of the dorsolateral prefrontal cortex at a locus which is activated in normal subjects during the internal generation of words. The disorganization syndrome, which has been shown to involve impaired suppression of inappropriate responses (eg in the Stroop test), is associated with increased perfusion of the right anterior cingulate gyrus at a location activated in normal subjects performing the Stroop test. The reality distortion syndrome, which evidence suggests arises from disordered internal monitoring of activity, is associated with increased perfusion in the medial temporal lobe at a locus activated in normal subjects during the internal monitoring of eye movements.

Introduction

The various psychotic conditions of young and middle adult life have characteristics in common, yet are clearly quite heterogeneous in clinical features and course. Kraepelin[1] recognized the importance of distinguishing manic depressive psychosis, which is episodic, from catatonia, hebephrenia and paranoia

Correspondence to: Dr P F Liddle, Department of Psychological Medicine, Hammersmith Hospital, DuCane Road, London W12 0HS

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